DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

CBER-04-012

August 9, 2004

VIA FACSIMILE AND CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WARNING LETTER

Dr. Barry Reit
Vice President
Regulatory Affairs & Quality Assurance
Novo Nordisk Pharmaceuticals, Inc.
100 College Rd. West
Princeton, NJ 08540

Re: BLA STN #103665
NovoSeven® [Coagulation Factor VIIa (Recombinant)]

Dear Dr. Reit:

The Advertising and Promotional Labeling Branch (APLB) in the Food and Drug Administration's Center for Biologics Evaluation and Research (CBER) has reviewed a patient guide (#127086, Tab 1), a flashcard (#126970, Tab 2), and a Spanish language patient brochure (#126946SP, submitted with an English translation of the content, Tab 3) for NovoSeven® [Coagulation Factor VIIa (Recombinant)] submitted by your firm under cover of Form FDA 2253. These materials violate Sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. §§ 352(a), 321(n)) because they fail to reveal material facts, make misleading safety claims, contain a representation or suggestion that a drug is useful in a broader range of conditions than has been demonstrated by substantial evidence or substantial clinical experience, and contain favorable results from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions. Cf. 21 CFR 202.1(e)(6)(i), (e)(7)(i). These materials thus could encourage the use of NovoSeven in conditions for which FDA has not found the product safe and effective.

Background

According to the FDA-approved professional labeling (PI), NovoSeven is a recombinant human coagulation Factor VIIa structurally similar to human plasma-derived Factor VIIa. NovoSeven is indicated for "the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or IX." As stated in the PI, "the largest number of patients who received NovoSeven during the investigational phase of product development were in an open protocol study." Accordingly, "clinical situations were diverse," dose schedules varied, and "[c]linical outcomes were not reported in a standardized manner."

The PI further states that NovoSeven is contraindicated in patients with known hypersensitivity to NovoSeven or any of the components of NovoSeven, and in patients with known hypersensitivity to mouse, hamster, or bovine proteins. The PI also contains warnings and precautions, with respect to the risk of thrombotic adverse events. In addition, it indicates that adverse reactions include fever, hemorrhage, decrease in plasma fibrinogen, hemarthrosis, and hypertension.

Failure to Reveal Material Facts

Page 9 of the patient guide describes NovoSeven as a treatment for hemophiliacs with inhibitors to Factor VIII and Factor IX, but does not disclose any risk information. As noted, NovoSeven is associated with several risks, including hypersensitivity reactions and thrombotic events. Although this information appears in the PI accompanying the patient guide, this is insufficient to make the effectiveness claim on page 9 truthful and non-misleading. Cf. 21 CFR 202.1(e)(3). The patient guide fails to reveal materials facts within the meaning of Section 201(n) of the Act and is, therefore, misleading under Section 502(a). 21 U.S.C. §§ 352(a), 321(n).

Misleading Safety Claim

The flashcard states, "Early administration of coagulation factor in patients with bleeding episodes can reduce pain and the risk of arthritis and permanent disability." To support this statement, the flashcard refers to the third-party website, http://www.hemophilia.org/bdi/bdi_newly2.htm, which states, "The quicker treatment (i.e. factor) is given, the more rapid the recovery. Other benefits are reduced pain and joint damage. When bleeding is well controlled, the risk of permanent damage and/or arthritis is reduced." Neither the flashcard nor the web site cites any study designed to permit a valid comparison between early and late treatment of bleeding episodes using NovoSeven. We are not otherwise aware of substantial evidence or substantial clinical experience substantiating this claim. The flashcard is, therefore, misleading under Section 502(a) of the Act (21 U.S.C. § 352(a)) because it contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is safer than has been demonstrated by substantial evidence or substantial clinical experience.

Unsubstantiated Effectiveness Claims

One side of the flashcard shows a large-font headline that states: "NovoSeven®: The recombinant clotting factor that universally induces hemostasis." The flashcard implies that NovoSeven® is effective in inducing hemostasis universally, in any patient, at any dose, and for any condition. In fact, as noted, NovoSeven is only indicated for the treatment of bleeding episodes in hemophilia A or B patients with inhibitors to Factor VIII or IX. We are unaware of substantial evidence or substantial clinical experience demonstrating that NovoSeven is effective in inducing hemostasis as the flashcard claims. If you have data substantiating this claim, please submit them to CBER for review.

The reverse side of the flashcard shows a large-font headline that states: "NovoSeven®: Clinical advantages with early treatment." The flashcard thus implies that NovoSeven is more effective when administered early in a bleeding episode than it is when administered late. We are not aware of substantial evidence or substantial clinical experience substantiating this claim. As stated in the PI, "the largest number of patients who received NovoSeven during the investigational phase of product development were in an open protocol study." Accordingly, "clinical situations were diverse," dose schedules varied, and "[c]linical outcomes were not reported in a standardized manner." The results from a randomized, double-blind comparison trial of two doses of NovoSeven do not provide substantial evidence to support a valid comparison of effectiveness between early and late treatment of bleeding episodes using NovoSeven. Without substantiation, this claim is false or misleading within the meaning of Section 502(a) of the Act (21 U.S.C. § 352(a)).

Page 13 of the Spanish language patient brochure states that "NovoSeven® controlled 92% of the bleeding in joints, muscles, and mouth." The flashcard similarly claims a "92% response rate in joint, muscle, and mucocutaneous hemorrhages." The cited study (Key, NS, Aledort, LM, Beardsley, D et al. *Thromb Haemost* 1998; 80:912-918) is not sufficient to substantiate this claim. In this study, subjects and their families performed enrollment, treatment, and the monitoring of outcomes using a clinical protocol that limited bleed severity and dose schedule. Therefore, the design of the study did not allow a determination of safety and efficacy for the purpose of product labeling. The flashcard and the Spanish language patient brochure are therefore false or misleading under 21 U.S.C. § 352(a) because they contain favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions. Cf. 21 CFR 202.1(e)(6)(i), (e)(7)(i).

Conclusion and Requested Action

The patient guide, flashcard, and patient brochure misbrand NovoSeven within the meaning of sections 502(a) and 201(n) of the Act (21 U.S.C. §§ 352(a), 321(n)) because they fail to reveal material facts, make misleading safety claims, contain unsubstantiated claims, and represent NovoSeven as more effective than has been demonstrated by substantial evidence or substantial clinical experience.

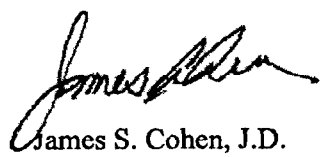
We request that Novo Nordisk immediately cease the dissemination of violative promotional materials for NovoSeven such as those described above. Please submit a written response to this letter within ten (10) business days of the date of this letter, stating whether you intend to comply with this request, listing all violative promotional materials for NovoSeven such as those described above, and explaining your plan for discontinuing use of such materials. Because the violations described above are serious, we request, further, that your submission include a plan of action to disseminate truthful, non-misleading, and complete information to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Biologics Evaluation and Research, Office of Compliance and

Biologics Quality, HFM-600, 1401 Rockville Pike, Rockville, Maryland 20852-1448. In all future correspondence regarding this matter, please refer to the BLA/STN number and to CBER-04-012. We remind you that only written communications are considered official responses.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for NovoSeven comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,



James S. Cohen, J.D.
Acting Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Enclosures
Tab 1 – Patient Guide
Tab 2 – Flashcard
Tab 3 – Patient Brochure